Radarins A-D: New Antiinsectan and Cytotoxic Indole Diterpenoids from the Sclerotia of *Aspergillus sulphureus*

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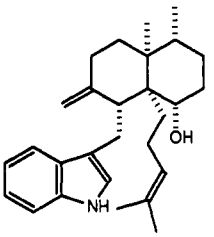
Four new indole diterpenoids, radarins A-D (**3-6**), have been isolated from the sclerotia of *Aspergillus sulphureus* by chromatographic separation of the CH_2Cl_2 extract. The structure of radarin A (**3**) was determined using extensive high-field 2D NMR experiments. Radarins B-D (**4-6**) were assigned by analysis of NMR data, spectral comparison to **3**, and/or by chemical interconversion. Compound **3** has the most potent activity against the corn earworm *Helicoverpa zea* and exhibits significant cytotoxicity in assays against three human solid tumor cell lines.

Chemical studies of the sclerotia of several *Aspergillus* spp. have resulted in the discovery of a variety of new natural products with antiinsectan activity or other biological effects.[1a-f] Most of these compounds are indole diterpenoids (e.g., **1** and **2**), and several of them contain previously undescribed or rare ring systems. Our continuing survey of these fungal bodies as sources of bioactive metabolites has led to the discovery of another new group of four compounds (**3-6**) with similar biogenetic origins from the sclerotia of *A. sulphureus* (Fres.) Thom and Church (NRRL 4077). The lead compound of the series, which we have named radarin A (**3**), exhibits significant activity against the corn earworm *Helicoverpa zea*, as well as cytotoxicity in assays against three human solid tumor cell lines. Details of the isolation, structure elucidation, and biological activities of these compounds are presented here.



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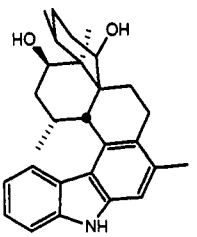

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A. sulphureus is a member of the *A. ochraceus* taxonomic group.[2] The strain chosen for investigation is the neotype strain on which the original species description was based (NRRL 4077 = WB 4077 = ATCC 16893 = IMI 211397).[2,3] Prior chemical studies of *A. sulphureus* have been limited, but it has been reported that this same strain produces ochratoxin A and penicillic acid when grown in liquid culture on a yeast extract-sucrose medium.[4] Sclerotia of *A. sulphureus* were produced by solid substrate fermentation on corn kernels. The methylene chloride extract of the ground sclerotia exhibited significant antiinsectan activity. The extract was separated first using silica gel column chromatography, and subsequently by reversed-phase HPLC to yield radarins A-D (**3-6**). The molecular formula of **3** was established as $C_{28}H_{39}NO_2$ (10 unsaturations) by analysis of HREIMS and ^{13}C NMR data. The mass spectrum contained a base peak at m/z 146 characteristic of a hydroxylated indole moiety, and signals for a 1,2,4-trisubstituted aromatic ring were also evident in the ^1H NMR spectrum. The ^{13}C NMR spectrum confirmed the presence of eight aromatic carbons, as expected for a hydroxylated indole, including a downfield-shifted (oxygenated) carbon signal at 153.9 ppm. The presence of a ketone functionality was indicated by the signal at 211.4 ppm. As no other carbon signals appeared beyond the aliphatic region, the remaining unsaturations must be accounted for by three additional rings.

Proton and carbon-13 NMR data for **3** are furnished in Tables I and II, respectively. Carbon-proton one-bond correlations were made by analysis of an inverse-detected heteronuclear multiple quantum coherence (HMQC)[5] experiment. Axial and equatorial proton dispositions were proposed on the basis of ^1H-^1H coupling constants when available. The location of the phenol functionality at C-6 and a second substituent at C-3 of the indole were assigned on the basis of a combination of homonuclear COSY and inverse-detected heteronuclear multiple bond correlation (HMBC)[6] data, along with comparison of the ^{13}C NMR shifts with those reported for other 6-oxygenated indoles.[7] An isolated methylene unit, two methyl doublets, and three methyl singlets were also evident in the ^1H NMR spectrum. Although the presence of several ethylene subunits could be determined by COSY correlations, unambiguous establishment of complete spin systems based on COSY data alone was hindered by significant overlap of signals in the ^1H NMR spectrum.

Most of the connectivity of **3** was assigned by interpretation of the HMBC experiment (Table III). Linkage of the isolated methylene (C-10) to C-3 of the indole moiety was straightforward, as the two corresponding protons were the only aliphatic signals to show correlations to any

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Table I. ^{1}H NMR Data for Radarins A–D (3–6)[a]

H no.	radarin A (3)	radarin B (4)	radarin C (5)	radarin D (6)
2	6.89 (br s)	6.88 (br s)	7.13 (br s)	7.08 (br s)
4	7.36 (d, 8.6)	7.38 (d, 8.5)	7.61 (br d, 8.0)	7.60 (d, 8.0)
5	6.63 (dd, 8.6, 2.2)	6.61 (dd, 8.6, 2.2)	7.00 (ddd, 8.0, 7.0, 1.0)	6.99 (ddd, 7.0, 7.0, 1.0)
6	–	–	7.07 (ddd, 8.0, 7.0, 1.0)	7.05 (ddd, 7.0, 7.0, 1.0)
7	6.78 (d, 2.1)	6.8 (d, 2.0)	7.38 (br d, 8.0)	7.36 (d, 8.1)
10a	2.74 (d, 15.1)	2.75 (d, 15.2)	2.83 (d, 15.0)	2.81 (d, 15.2)
b	2.65 (d, 15.1)	2.66 (d, 15.1)	2.76 (d, 15.2)	2.72 (d, 15.1)
12ax	1.57 (m)	1.52 (m)	1.60 (m)	1.57 (m)
13ax	1.39 (m)	1.38 (m)	1.42 (m)	1.38 (m)
eq	1.25 (m)	1.21 (m)	1.30 (m)	1.21 (m)
14ax	0.71 (m)	0.58 (dm, 3.9)	0.73 (m)	0.58 (ddd, 13.0, 13.0, 3.8)
eq	1.58 (m)	1.58 (m)	1.62 (m)	1.60 (m)
16ax	1.28 (m)	0.64 (dd, 11.7, 1.9)	1.36 (m)	0.62 (dd, 12.0, 1.8)
17ax	1.83 (m)	1.50 (m)	1.87 (m)	1.50 (m)
eq	1.54 (m)	1.30 (m)	1.56 (m)	1.30 (m)
18ax	2.22 (m)	1.40 (m)	2.32 (m)	1.40 (m)
eq	2.13 (m)	1.76 (m)	2.25 (m)	1.78 (m)
19eq	–	3.62 (m)	–	3.61 (dm, 2.6)
20ax	2.10 (m)	1.07 (m)	2.09 (m)	1.06 (m)
22ax	1.20 (m)	0.95 (m)	1.22 (m)	0.95 (ddd, 12.8, 12.8, 3.7)
eq	1.72 (ddd, 12.9, 3.3, 3.2)	1.76 (m)	1.76 (dm, 12.9)	1.76 (m)
23ax	1.50 (m)	1.45 (m)	1.52 (m)	1.45 (m)
eq	1.96 (m)	1.89 (dm, 13.5)	2.0 (m)	1.89 (dm, 16.6)
24ax	1.10 (dd, 11.9, 1.9)	1.04 (m)	1.11 (dd, 12.0, 1.8)	1.03 (dm, 1.8)
25	0.82 (s)	0.83 (s)	0.88 (s)	0.86 (s)
26	1.02 (d, 6.7)	1.04 (d, 7.5)	1.08 (d, 6.6)	1.05 (d, 6.5)
27	0.86 (s)	0.89 (s)	0.91 (s)	0.89 (s)
28	0.74 (d, 6.7)	0.92 (d, 7.2)	0.78 (d, 6.7)	0.90 (d, 7.1)
29	0.68 (s)	1.02 (s)	0.72 (s)	1.02 (s)

[a] Data were recorded in acetone-d_6 at 600 MHz.

Table II. ^{13}C NMR Data for Radarins A–D (3–6)[a]

C no.	radarin A (3)	radarin B (4)	radarin C (5)	radarin D (6)
2	123.2	123.0	125.0	124.8
3	112.2	112.2	112.2	112.3
4	120.2	120.2	119.8	119.8
5	109.8	109.7	119.3	119.2
6	153.9	153.8	121.7	121.6
7	97.4	97.3	112.1	112.0
8	138.1	138.1	137.0	136.9
9	124.1	124.2	130.1	130.2
10	34.5	34.3	34.3	34.2
11	41.3	41.3	41.3	41.4
12	36.8	36.7	36.8	36.8
13	28.1	28.2	28.1	28.2
14	40.2	40.2	40.2	40.3
15	38.7	38.3	38.4	38.3
16	59.3	61.9	59.3	62.0
17	22.8	16.6	22.8	16.7
18	41.7	36.5	41.7	36.5
19	211.4	71.8	211.5	71.7
20	58.3	50.3	58.2	50.3
21	42.1	38.4	42.1	38.4
22	41.0	41.7	41.0	41.8
23	19.7	19.1	19.7	19.1
24	51.1	51.3	51.2	51.4
25	18.1	17.9	18.1	17.9
26	17.6	17.7	17.6	17.7
27	16.8	17.1	16.7	17.1
28	7.2	12.2	7.1	12.2
29	15.0	17.0	15.0	17.1

[a] Data were recorded in acetone-d_6 at 75.6 or 90.7 MHz.

Table III. HMBC and NOESY Data for Radarin A (3)[a]

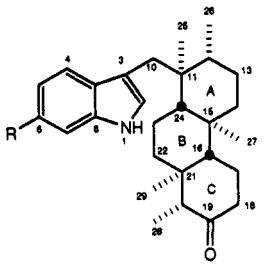
H no.	selective INEPT and/or HMBC correlations	NOESY correlations
2	3, 8, 9	10a, 23eq, 24ax, 26
4	3, 6, 8	10b
5	6,[b] 7, 9	
7	5, 6, 9	
10a	2, 3, 9, 11, 12	2
10b	2, 3, 9, 11, 12, 24	4, 25, 26
13ax	12,[c] 14,[c] 26[c]	25, 27
16ax		20ax, 24ax
17ax	15,[b], 16,[b] 18,[b] 19,[b] 21	
18ax	16, 17, 19	20ax
18eq	16, 17, 20	
20ax	16, 19, 21, 22, 28, 29	16ax, 18ax, 22ax
22ax	20,[c], 21,[c] 23,[c], 29[c]	20ax, 24ax
22eq	16, 21, 23,[c] 24, 29	28, 29
23eq	11,[b] 15,[b] 21,[b] 22,[b] 24[b]	2
24ax	10,[c], 11, 14,[c] 15, 16,[c] 22,[b] 23, 25, 27	2, 16ax, 22ax
25	10, 11, 12, 24	10b, 13ax, 26, 27
26	11, 12, 13	2, 10b, 25
27	14, 15, 16, 24	13ax, 25, 29
28	19, 20, 21	22eq, 29
29	16, 20, 21, 22	22eq, 27, 28

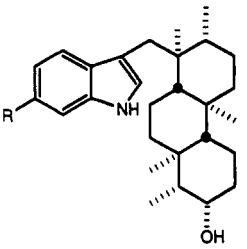
[a] Data were recorded in acetone-d_6. All HMBC and/or selective INEPT correlations represent 2- or 3-bond couplings. NOESY correlations between scalar-coupled protons have been omitted. [b] Correlations observed only in selective INEPT experiments. [c] Correlations observed only in the HMBC experiment.

aromatic carbons (i.e. carbons 2, 3, and 9). The only other cross-peaks for these protons corresponded to carbons 11, 12, and 24. Since the methyl singlet for C-25 correlates with C-10 as well as C-11, -12, and -24, carbons 10 and 11 could be connected. The upfield-shifted methine proton signal at 1.10 ppm (attached to C-24) was well-resolved and provided several key correlations. Connection of C-24 to C-11 was confirmed by correlations of H-24 to both C-11 and C-25. The ethylene unit comprising carbons 22 and 23 could also be attached to C-24 based on COSY correlations. Carbon 21 was linked to carbon 22 because the methyl proton singlet at 0.68 ppm (H_3-29) showed HMBC correlations to both C-21 and C-22. The well-resolved nature of the downfield-shifted signals of the protons α to the carbonyl group allowed for assignment of the unit comprising carbons 16–21 based on the COSY, HMBC, and HMQC data. Moreover, observation of an HMBC correlation between the H_3-29 proton signal and the methine carbon C-16 revealed the linkage of C-16 to C-21 to form a six-membered ring. Since the methyl singlet at 0.91 ppm (H_3-27) correlated with only one quaternary

carbon (C-15) and with C-16, both the methyl group and C-16 could be attached to C-15. The same methyl proton signal also showed a correlation with C-24 and C-14, allowing connections to be made between C-15 and C-24 and between C-15 and the ethylene unit consisting of C-13 and C-14. The methyl proton doublet at 1.02 ppm (H_3-26) was correlated to both C-11 and the other carbon of the C-13–C-14 ethylene unit (C-13), thus completing the gross structure of radarin A and permitting its assignment as **3**.

Further studies of the same extract led to the isolation of three closely related analogues of **3** (**4**–**6**). The mass spectrum of radarin B (**4**) has the same base peak as **3** (m/z 146) but indicated a molecular weight two mass units higher. The expected molecular formula of $C_{28}H_{41}NO_2$ was confirmed by HREIMS. The ^{13}C NMR spectra of **3** and **4** are very similar. The absence of the ketone signal at 211.4 and the appearance of a new signal at 71.8 suggest that **4** has a secondary hydroxyl group in place of the ketone functionality. The ^{13}C NMR shifts for the carbons of **4** are virtually identical to those of **3** (±1.0 ppm) except for those α and β to the oxygenated carbon (Table II). The two α carbons, C-18 and C-20, shift from 41.7 and 58.3 ppm in **3** to 36.5 and 50.3 ppm in **4**. The three carbons β to the site of oxygenation are shifted from 22.8 to 16.6, 42.1 to 38.4, and 7.2 to 12.2 ppm. A small shift (+2.5 ppm) also occurs in C-16. These differences are consistent with the change in ^{13}C NMR substituent effects upon replacement of a carbonyl with an hydroxyl group.[8] The structure of **4** was verified by a COSY experiment and a series of selective INEPT[9] experiments. Because overlap in the proton spectrum of **4** was more severe than in **3**, additional confirming evidence was sought by chemical interconversion of **4** and **3**. Although several sets of oxidation conditions were unsuccessful, **3** was ultimately reduced to **4** with L-Selectride (Aldrich).





3 R = OH **4** R = OH

5 R = H **6** R = H

The two remaining analogues (**5** and **6**) both yield mass spectra that exhibit a base peak of m/z 130, which is characteristic of a 3-substituted indole moiety. This observation is in accord with the presence of ortho-disubstitution patterns in the ^1H NMR spectral data for both compounds (Table I). Radarin C (**5**) has the molecular formula $C_{28}H_{39}NO$ as evidenced by HREIMS, while radarin D (**6**) has two additional hydrogen atoms. The ^{13}C NMR spectra of **5** and **3** are nearly identical except for the aromatic region (Table II). The aromatic carbon shifts for **5** are typical of a 3-substituted indole.[1a-c,7] Likewise, the ^{13}C NMR spectrum of **6** differs little from the ^{13}C NMR spectrum of **4** except for the indole signals, which are

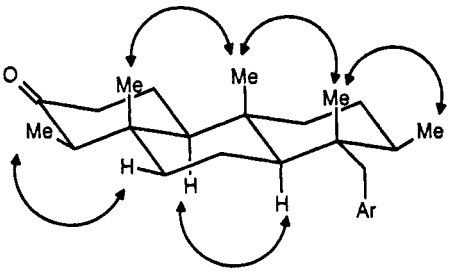


Figure 1. Selected NOESY correlations for radarin A (**3**).

within 0.5 ppm of the ^{13}C NMR shifts for the aromatic carbons of **5** (Table II). Thus, the structures of **5** and **6** were assigned as shown, differing from **3** and **4** only in the absence of a phenolic OH group.

The relative stereochemistry of radarin A was proposed based on analysis of the NOESY data provided in Table III. All methylene and methine ring protons could be assigned as axial or equatorial by examination of ^1H–^1H coupling constants. The axial or equatorial dispositions of the methyl groups were decided based on their NOESY interactions with other protons (Figure 1). The methyl group attached to C-20 (H_3-28) must be in an equatorial position since it has an NOE interaction with the equatorial proton on C-22. Strong NOESY correlations between H_3-29 and H_3-27 and between H_3-27 and H_3-25 indicate 1,3-diaxial interactions. Hence, these three methyl groups must be on the same face of the ring system and in axial positions. Because there is a NOESY correlation between H_3-25 and H_3-26, H_3-26 must be in an equatorial position, making the two methyls cis to each other. The axial methine proton H-24 shows a NOESY correlation with H-16 which also represents a 1,3-diaxial interaction. This 1,3-diaxial association together with the strong correlation between H_3-27 and H_3-29 clearly demonstrate that both of the ring fusions in the tricyclic ring system are trans. Other NOESY correlations support the proposed relative stereochemistry as depicted in **3**. Dreiding molecular models suggest that the three rings must exist in chair conformations. If ring A were in a boat conformation, H_3-26 would be very unlikely to show a NOESY correlation with either proton on C-10, since C-26 and C-10 would be separated by a vicinal angle of nearly 180°. The 1,3-diaxial NOESY interaction between H-22ax and H-24ax suggests that the B ring also must be in a chair conformation. Ring C cannot be in a boat conformation because H-18ax and H-20ax show a strong NOESY correlation (1,3-diaxial interaction). The stereochemistry of the hydroxyl group in radarins B and D must be axial, as the proton on C-19 lacks a large (diaxial) $^3J_{HH}$ value. The remaining stereochemical assignments for **4**–**6** were made by analogy to **3**. A stereoselective reduction of **3** to **4** provided further confirming evidence for the stereochemical relationship of **3** and **4**.

Because radarins A and C possess substituted cyclohexanone moieties, the circular dichroism (CD) spectra were examined in an effort to propose absolute stereochemistry. The octant rule relates the sign and amplitude of the Cotton effect for a ketone carbonyl group in a cyclohexanone ring in the chair conformation to the spatial orientation of the atoms near the ketone.[10] Both radarins A and C yield CD spectra with negative differential dichroic absorptions at 290 nm for the ketone carbonyl chromophore. Upon projection of the two possible enantiomers into octants (given the proposed relative stereo-

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chemistry), the sign of the CD spectrum in the region of the carbonyl absorption suggests that the absolute stereochemistry of the radarins be proposed as shown in **3–6**. As expected, radarins B and D lack the corresponding absorption. Radarins A–D most likely arise biogenetically via cyclization of geranyl geranyl indole accompanied by rearrangement of two methyl groups.

Radarin A induces a 52.7% reduction in weight gain relative to controls after 1 week when incorporated into a standard test diet of the corn earworm *Helicoverpa zea* (formerly *Heliothis zea*)[11] at 100 ppm. Radarin C also exhibits some activity at the same concentration, causing a weight gain reduction of 17.1%, while radarins B and D are inactive in this assay at 100 ppm. Further biological evaluation revealed that radarin A is active toward human lung carcinoma A549, breast adenocarcinoma MCF7, and colon adenocarcinoma HT-29 cells with ED_{50} values of 2.5, 5.5, and 1.9 μg/mL, respectively.[12] Radarin B possesses comparable activity in these three cell lines, affording ED_{50} values of 2.0, 2.0, and 0.7 μg/mL, respectively.

Experimental Section

General. A culture of *A. sulphureus* (NRRL 4077) was obtained from the Agricultural Research Service (ARS) collection at the USDA Center for Agricultural Utilization Research in Peoria, IL. The sclerotia were produced by solid substrate fermentation on autoclaved corn kernels using general procedures that are described elsewhere.[1a,13] The harvested sclerotia were then ground to a powder with a Tecator mill (Perstorp Instrument Co.) before storing at 4 °C until extraction. HMBC and HMQC NMR data were obtained at 600 MHz. Chemical shifts were recorded in acetone-d_6 using the corresponding solvent signals (2.04 ppm for ^1H and 29.8 ppm for ^{13}C) as references. DEPT experiments were used to determine carbon multiplicities, which are in agreement with the carbon assignments. Long-range CH correlations were established using the HMBC experiment optimized for $^nJ_{CH}$ = 8.3 Hz and/or selective INEPT experiments optimized for $^nJ_{CH}$ values of 4, 7, or 10 Hz. Other details regarding bioassays and experimental procedures have appeared elsewhere.[1a-f]

Isolation and Properties of Radarins A–D (3–6). Ground sclerotia of *A. sulphureus* (NRRL 4077, 150.0 g) were exhaustively extracted using a soxhlet apparatus first with pentane and then with methylene chloride. The methylene chloride extract (1.5 g) was subjected to silica gel column chromatography, using a stepwise gradient from 0 to 10% (v/v) MeOH in $CHCl_3$. Fractions of similar composition as determined by TLC were pooled. The resulting active fractions were separated further by reversed-phase HPLC (5-μm Beckman Ultrasphere ODS column; 250 × 10 mm; UV detection at 215 nm; flow rate 2.0 mL/min) using various MeOH–H_2O mixtures to yield compounds **3** (15.1 mg), **4** (37.2 mg), **5** (8.0 mg), and **6** (4.4 mg).

Radarin A (3) was isolated as a pink oil with the following properties: $[\alpha]_D$ +11.1° (*c* 0.005, $CHCl_3$); HPLC t_R 25.5 min (88:12 MeOH–H_2O); UV (MeOH) 210 (ε 6222), 226 (6985), 290 (1512); CD (MeOH) 290 nm (Δε −78.6), 233 (−31.9), 216 (−34.3); IR 3405, 2925, 2956, 1700, 1628, 1452, 757 cm^{-1}; ^1H and ^{13}C NMR data, Tables I and II, respectively; HMBC and NOESY data, Table III; EIMS (70 eV) 421 (M^+, rel int 4.3), 189 (4.2), 175 (2.6), 161 (3.7), 146 (100), 123 (6.6), 121 (9.3), 119 (5.8), 109 (8.0), 107 (9.0), 105 (7.0); HREIMS obsd 421.2996, calcd for $C_{28}H_{39}NO_2$ 421.2981.

Radarin B (4): yellow solid; mp 115–118 °C (dec); $[\alpha]_D$ +39.4° (*c* 0.003, $CHCl_3$); HPLC t_R 22.2 min (86:14 MeOH–H_2O); CD (MeOH) 228 nm (Δε −64.2); IR 3408, 2927, 2856, 1628, 1453, 1384, 757 cm^{-1}; ^1H and ^{13}C NMR data, Tables I and II, respectively; EIMS (70 eV) 423 (M^+, rel int 1.3), 405 (3.8), 243 (7.7), 163 (11), 147 (100), 121 (19), 107 (22), 91 (28), 81 (22); HRFABMS obsd 424.3245, calcd for $C_{28}H_{41}NO_2$ + H, 424.3215.

Radarin C (5): yellow oil; $[\alpha]_D$ +6.7° (*c* 0.002, $CHCl_3$); HPLC t_R 40 min (90:10 MeOH–H_2O); CD (MeOH) 290 nm (Δε −58.7), 229 (−36.7), 212 (+68.4); IR 3410, 2925, 2857, 1707, 1456, 1388, 741 cm^{-1}; ^1H and ^{13}C NMR data Tables I and II, respectively; EIMS (70 eV) 405 (M^+, rel int 2.0), 137 (2.2), 130 (100), 121 (3.2), 111 (3.3), 109 (3.2), 107 (3.5); HREIMS obsd 405.3008, calcd for $C_{28}H_{39}NO$ 405.3032.

Radarin D (6): yellow oil; $[\alpha]_D$ +31.8° (*c* 0.003, $CHCl_3$); HPLC t_R 45 min (90:10 MeOH–H_2O); CD (MeOH) 228 nm (Δε −58.0); IR 3414, 2924, 2856, 1456, 1384, 742 cm^{-1}; ^1H and ^{13}C NMR data, Tables I and II, respectively; EIMS (70 eV) 407 (M^+, rel int 0.5), 389 (1.7), 163 (4.3), 149 (5.5), 131 (100), 121 (6.9), 111 (7.1), 109 (5.1), 107 (6.9); HREIMS obsd 407.3176, calcd for $C_{28}H_{41}NO$ 407.3188.

Reduction of 3 to 4. L-Selectride (45 μL of a 1.0 M solution in THF) was added to a 2-mL reaction vial at −78 °C containing 2.0 mg of **3** in 1.0 of mL of dry THF. After the mixture was stirred for 30 min at −78 °C, H_2O (50 μL) was added and the mixture was allowed to warm to rt (15 min). Anhydrous $MgSO_4$ was added, and the solution was then passed through a small silica column. The product obtained upon evaporation of the solvent was redissolved in 1.0 mL of CH_2Cl_2 and extracted with H_2O (5 × 1 mL). The organic phase was dried and evaporated to yield **4** (1.9 mg, 95% yield), which was identical to the natural product based on ^1H NMR and HPLC analysis.

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Supplementary Material Available: ^1H NMR spectra for radarins A–D (4 pages). Ordering information is given on any current masthead page.

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